REMARKS

Applicants respectfully request reconsideration and reexamination of this application.

Claims 23, 32, and 33 are pending.

Claims 23, 32, and 33 have been amended to recite three nucleic acid fragments of the HIV-1 genome contained in plasmid λ-J19. The fragments, when inserted in an expression vector and expressed in an expression system, produce recombinant antigens of HIV-1. The fragment of claim 23 extends from the restriction site *Kpn*I at about coordinate 6100 to the restriction site *Bgl*II at about coordinate 9150, and corresponds at least in part to the *env* gene. Specification at page 4, line 30 through page 5, line 2. The fragment of claim 32 extends from the restriction site *Kpn*I at about coordinate 3500 to the restriction site *Bgl*II at about coordinate 6500, and corresponds at least in part to the *pol* gene. Specification at page 5, lines 3-5. Finally, the fragment of claim 33 extends from the restriction site *Pst*I at about coordinate 800 to the restriction site *Kpn*I at about coordinate 3500, and corresponds at least in part to the *gag* gene. Specification at page 5, lines 6-9. Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

The invention is directed to a method of producing antibodies to antigens of HIV-1. The antigens correspond to the expression products of a host transformed with a vector containing a nucleic acid fragment of plasmid λ-J19. The

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nucleic acids are fragments of plasmid λ-J19 that encode *env*, *gag*, and *pol* antigens of HIV-1. Specification at page 4, line 30 through page 5, line 9. The antibodies are useful, for example, as reagents in screening assays to detect recombinantly produced antigenically competent fusion proteins. Specification at page 13, lines 30-33.

Withdrawal of the rejection of claim 23 under 35 U.S.C. § 101 for lack of patentable utility, in view of applicants' amendment to claim 23 adding a recovery step for the antibodies, is acknowledged.

I. Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph

Claims 23 and 32-33 were rejected under 35 U.S.C. § 112, first paragraph, as the specification as originally filed does not provide support for the invention as now claimed. Applicants respectfully traverse this ground for rejection.

Support for the nucleic acids recited in the amended claims is given above. Support for using the nucleic acid identified by applicants for expression of viral antigens is given at, for example, page 13, lines 13-19. Finally, support for antibodies against viral antigens is given at, for example, page 13, lines 30-33.

A. Techniques Known in the Art Need Not be Described in the Specification to Enable the Claimed Invention

Applicants argued in the Amendment filed February 9, 1994 that because techniques of producing antibodies were known in the art at the time the claimed invention was made, specific descriptions of such techniques are not required to enable the

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present invention. In support of this argument, applicants cited In re Strahilevitz, 212 U.S.P.Q. 561, 564 (C.C.P.A. 1982).

In response to applicants' arguments, the Examiner maintained the rejection because

> the specification fails to set forth a methods [*sic*, method] of producing or raising antibodies with the recited steps, i.e. providing the expression product, raising the antibodies and recovering said antibodies. . . . No where in the specification is a method with [the] claimed step of recovering antibodies set forth. Accordingly, the as-filed specification provides no evidence of conception of the invention as now claimed.

Paper No. 8 at 3. Applicants respectfully disagree.

The specification need not include that which is already known by and available to the public. Paperless Accounting, Inc. v. Bay Area Rapid Transit System, 804 F.2d 659, 664, 231 U.S.P.Q. 649, 653 (Fed. Cir. 1986). In fact, techniques that were old and well-known when the application was filed need not be included in the specification, and are preferably omitted. Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534, 3 U.S.P.Q. 2d 1737 (Fed. Cir. 1987).

An Examiner may properly lodge a rejection of claims as based on a specification that is not in compliance with § 112, first paragraph, if it appears reasonable to conclude that one skilled in the art would have been unable to make or use the invention at the time the application was filed. When that conclusion is reasonable, the burden is on the applicant to rebut it, if he can, such as by offering evidence. In re Eynde, 178 U.S.P.Q. 470, 474 (C.C.P.A. 1975).

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The patent applicant can carry this burden by showing that a person of ordinary skill in the art possessed of the knowledge available at the time of filing could practice the invention without undue experimentation. Id. "A patent applicant may offer evidence, such as patents and publications, to show the knowledge possessed by those skilled in the art and thereby establish that a given specification disclosure is enabling." Id.; emphasis added.

Conversely, if the information required to practice the invention is not well-known in the art, the application itself must contain the information. In re Buchner, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). Thus, if applicants had to rely on unknown or unconventional techniques for carrying out their invention, their patent application would have to describe these techniques. This is not such a case.

Applicants, while maintaining that the specification is in compliance with § 112, first paragraph, provided the Examiner with "publications" to show that a person of ordinary skill in the art would know how to produce, isolate, and use the antibodies produced by the claimed method at page 7 of the Amendment filed February 9, 1994. In accordance with Federal Circuit precedent, this subject matter need not be described in the specification. As stated by the court in In re Bosy, 149 U.S.P.Q. 789, 792 (C.C.P.A. 1966): "That which is common and well known is as if it were written out in the patent."

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B. The Specification Identifies Antigens of HIV-1, and the Claims Have Been Amended to Recite These Antigens of HIV-1

Continuing, the Examiner stated that

> [t]he specification teaches only the isolation and rough restriction map of the J-19 clone. . . . The specification fails to teach the identity of any encoded antigen, does not teach the location of any open reading frame contained within the clone, does not teach the sequence of the DNA that would enable the skilled artisan to locate potential open reading frames . . .

Paper No. 8 at pages 3-4. Applicants respectfully disagree.

Claims 23, 32, and 33 have been amended to recite a method of producing antibodies to antigens of HIV-1 type by employing nucleic acid from plasmid λ-J19. The nucleic acids correspond to *gag*, *pol*, and *env* antigens of HIV-1. Because applicants identify the approximate location of the *env*, *gag*, and *pol* genes on the HIV-1 genome contained in plasmid λ-J19, applicants describe and enable the claimed invention directed to a method of producing antibodies against antigens of HIV-1.

Specifically, the nucleic acid of claim 23 extends from the restriction site *Kpn*I at about coordinate 6100 to the restriction site *Bgl*II at about coordinate 9150 of the HIV-1 genome of plasmid λ-J19. Specification at page 4, line 30 through page 5, line 2. Because this nucleic acid corresponds to a portion of the *env* gene of HIV-1, a recombinant *env* antigen of HIV-1 is produced when a recombinant vector containing this nucleic acid is expressed in a expression system.

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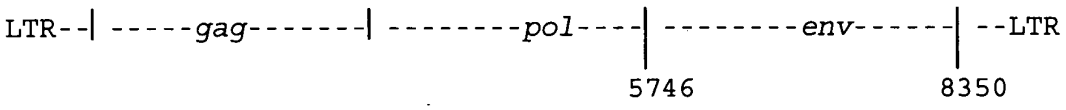
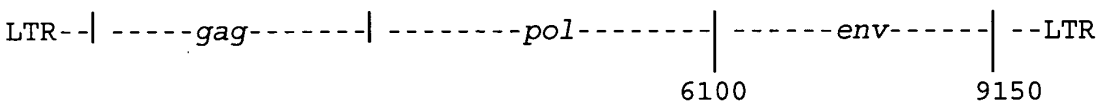
This conclusion is supported by Wain-Hobson et al., Nucleotide Sequence of the AIDS Virus, LAV," Cell, 40, 9-17 (1985) (Exhibit 1). This reference gives the complete nucleotide sequence of the HIV-1 genome of plasmid λ-J19. At page 12, Wain-Hobson et al. teach that the first triplet of the *env* gene is at nucleotide 5746, that the first methionine (start of translation) is at nucleotide 5767, and that the stop codon is at nucleotide 8350.

The following chart shows the location of the *env* gene taught by Wain-Hobson et al. and the location of the *env* fragment taught by applicants.

Location of *env* gene of HIV-1 according to Wain-Hobson et al.:



Location of a fragment of the *env* gene of HIV-1 according to applicants:



Applicants' fragment does not correspond to the complete *env* gene of HIV-1. However, this is not required by the claims. The claims recite an antigen of HIV-1. When the fragment recited in the claims is inserted into a vector and expressed in an expression system, a recombinant *env* antigen is produced. The recombinant antigen corresponds to the portion of the *env* gene extending from the restriction site *Kpn*I at about coordinate 6100 to the stop codon at coordinate 8350.

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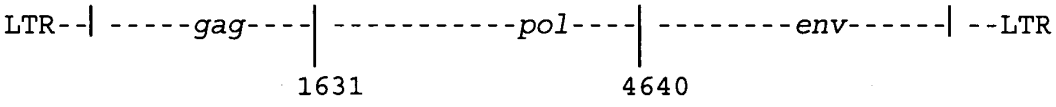
The nucleic acid fragment of claim 32 extends from the restriction site *Kpn*I at about coordinate 3500 to the restriction site *Bgl*II at about coordinate 6500 of the HIV-1 genome of plasmid λ-J19. Specification at page 5, lines 3-5. Because this nucleic acid corresponds to a portion of the *pol* gene of HIV-1, a recombinant *pol* antigen of HIV-1 is produced when a recombinant vector containing this nucleic acid is expressed in a expression system.

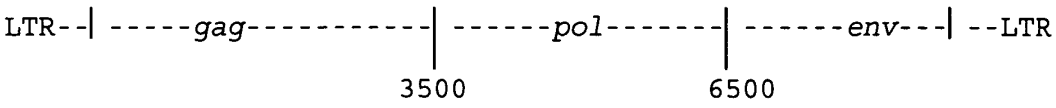
This conclusion is supported by Wain-Hobson et al., who teach that the first triplet of the *pol* gene is at nucleotide 1631, that the first methionine (start of translation) is at nucleotide 1934, and that the stop codon is at nucleotide 4640. Wain-Hobson et al. at 12.

The following chart shows the location of the *pol* gene taught by Wain-Hobson et al. and the location of the *pol* fragment taught by applicants.

Location of *pol* gene of HIV-1 according to Wain-Hobson et al.:



Location of a fragment of the *pol* gene of HIV-1 according to applicants:



Applicants' fragment does not correspond to the complete *pol* gene of HIV-1. However, this is not required by the claims. The claims recite an antigen of HIV-1. When the fragment recited in the claims is inserted into a vector and expressed in

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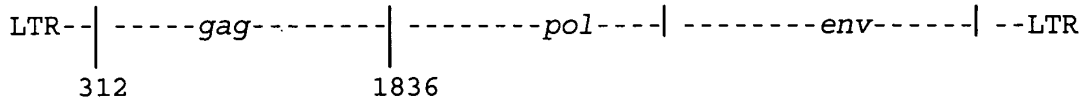
an expression system, a recombinant *pol* antigen is produced. The recombinant antigen corresponds to the portion of the *pol* gene extending from the restriction site *Kpn*I at about coordinate 3500 to the stop codon at coordinate 4640.

The nucleic acid fragment of claim 33 extends from the restriction site *Pst*I at about coordinate 800 to the restriction site *Kpn*I at about coordinate 3500 of the HIV-1 genome of plasmid λ-J19. Specification at page 5, lines 6-9. Because this nucleic acid corresponds to a portion of the *gag* gene of HIV-1, a recombinant *gag* antigen of HIV-1 is produced when a recombinant vector containing this nucleic acid is expressed in an expression system.

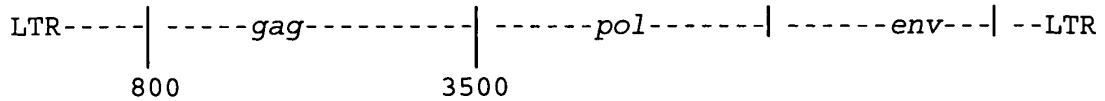
This conclusion is supported by Wain-Hobson et al., who teach that the first triplet of the *gag* gene is at nucleotide 312, that the first methionine (start of translation) is at nucleotide 336, and that the stop codon is at nucleotide 1836. Wain-Hobson et al. at 12.

The following chart shows the location of the *gag* gene taught by Wain-Hobson et al. and the location of the *gag* fragment taught by applicants.

Location of *gag* gene of HIV-1 according to Wain-Hobson et al.:



Location of a fragment of the *pol* gene of HIV-1 according to applicants:



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Applicants' fragment does not correspond to the complete *gag* gene of HIV-1. However, this is not required by the claims. The claims recite an antigen of HIV-1. When the fragment recited in the claims is inserted into a vector and expressed in an expression system, a recombinant *gag* antigen is produced. The recombinant antigen corresponds to the portion of the *gag* gene extending from the restriction site *Pst*I at about coordinate 800 to the stop codon at coordinate 1836.

C. Working Examples are not Required Where the Specification is Otherwise Enabling

Finally, the Examiner stated that the specification

> does not teach the expression of any single antigen. Even if the skilled artisan possessed knowledge as to the open reading frames contained within the J-19 clone, the successful expression of a protein in an antigenically relevant form is often problematic. . . . The cited references (Exhibits 1-3) merely teach the general methods of raising antibodies and producing monoclonal antibodies. The references do not teach how to arrive with the first step of the claimed methods, i.e. providing the instant antigen.

Paper No. 8 at page 4. Applicants courteously disagree.

The absence of a working example, denominated as such, does not compel the conclusion that a specification does not satisfy the requirements of 35 U.S.C. § 112. In re Long, 151 U.S.P.Q. 640, 642 (C.C.P.A. 1966). This principle is so firmly established in patent practice that it should be unnecessary to cite legal authority.

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The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention. Lindemann Machinenfabrik GMBH v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984). The specification need not include that which is already known by and available to the public. Paperless Accounting, Inc. v. Bay Area Rapid Transit System, 804 F.2d 659, 664, 231 U.S.P.Q. 649, 653 (Fed. Cir. 1986). In fact, techniques that were old and well-known when the application was filed need not be included in the specification, and are preferably omitted. Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534, 3 U.S.P.Q. 2d 1737 (Fed. Cir. 1987).

Because expression techniques were known in the art at the time the claimed invention was made, such techniques need not be described in the specification to satisfy 35 U.S.C. § 112, first paragraph.

For example, Maniatis et al., Molecular Cloning; A Laboratory Manual (Cold Spring Harbor Laboratory, 1982) (Exhibit 2) describes synthesis, cloning, and isolation of cDNA at pages 213-246. Introduction of plasmid and bacteriophage λ DNA into *Escherichia coli* is described at pages 246-255; three techniques for identifying recombinant clones are described at pages 310-361; and subcloning of small DNA fragments into plasmid vectors is described at pages 390-401 of Maniatis et al. Expression techniques are also described in Old et al., Principles of Gene Manipulation; An Introduction to Genetic Engineering, Third Edition, pages 3-44 (1985) (Exhibit 3).

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In support of this argument, the Examiner cited Kamtekar et al., which "addresses some of the problems associated with the over-expression of heterologous proteins that still plagued researchers in 1993." Paper No. 8 at page 4.

Kamtekar et al., "Protein Design by Binary Patterning of Polar and Nonpolar Amino Acids," Science, 262, 1680-1685 (1993), describe a general strategy for the *de novo* design of protein sequences. Kamtekar et al. at 1680. The described method requires the explicit sequence location of the polar and nonpolar residues. Kamtekar et al. at 1680; and Fig. 2 at 1681. This reference does not describe difficulties with expressing nucleic acid in recombinant expression systems. Rather, the reference refers to designing *de novo* synthetic proteins.

Given the novel fragments of HIV-1 disclosed by applicants, and given the restriction sites at the ends of each fragment, the fragments can be cloned using techniques well known in the art at the time the claimed invention was made. Because the nucleic acids recited in claims 23, 32, and 33, when expressed in a recombinant molecule, produce antigens of HIV-1, the claimed invention is enabled for methods of producing antibodies against antigens of HIV-1. Withdrawal of this ground for rejection is respectfully requested.

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II. **Rejection of the Claims under 35 U.S.C. § 102(b)**

Claims 23, 32, and 33 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by any one of Robey et al., Proc. Natl. Acad. Sci. USA, 83, 7023-7027 (1986), Rusche et al., Proc. Natl. Acad. Sci. USA, 84, 6924-6928 (1987), Lasky et al., Science, 233. 209-212 (1986), Chanh et al., The EMBO Journal, 5, 3065-3071 (1986), or Putney et al., Science, 234, 1392-1395 (1986).

Applicants argued in the Amendment filed February 9, 1994 that they are entitled to priority of GB 84 23659, filed September 19, 1984. Because Robey et al., Rusche et al., Lasky et al., Chanh et al., and Putney et al. were all published after applicants' claimed priority date of September 19, 1984, these references are not available as prior art against this application.

In response, the Examiner stated that

> [t]his argument has been carefully considered but is found unpersuasive for the reasons set forth above, i.e. the specification does not provide support for the invention as now claimed. Accordingly, the priority date awarded to the claims 23 and 32-33 is that of the instant application and the above rejection under 35 U.S.C. § 102(b) is maintained.

Paper No. 8 at page 6. Applicants courteously disagree.

Support for the nucleic acids recited in the amended claims is given above. Support for using the nucleic acid identified by applicants for expression of viral antigens is given at, for

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example, page 13, lines 13-19. Finally, support for antibodies against viral antigens is given at, for example, page 13, lines 30-33. Because applicants' specification, which is identical to GB 84 23659, filed September 19, 1984, provides support for the claimed invention, the cited references are not available as prior art against this application. Withdrawal of this ground for rejection is respectfully requested.

It is acknowledged that this Amendment is submitted after final rejection of the claims. However, because this Amendment places the application in condition for allowance, entry thereof by the Examiner is courteously requested.

Reconsideration and reexamination of this application, and allowance of the pending claims are respectfully requested.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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By: Michele M Schafer
Michele M. Schafer
Reg. No. 34,717

Date: December 6, 1994

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